Welcome to Yale Cancer Answers with your host doctor Anees Chagpar. Yale Cancer Answers features the latest information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week, it’s a conversation about prostate cancer with Doctor Peter Humphrey. Doctor Humphrey is a professor of pathology at Yale School of Medicine, where Doctor Chagpar is a professor of surgical oncology. Peter, maybe we can start off by you telling us a little bit about yourself and what you do. I’m a practicing surgical pathologist which basically means that I look at a glass slide under a microscope and render a diagnosis, often cancer diagnosis on tissues that we received from other physicians, including biopsies and and resections, so microscopes have always interested me. Ever since I was very young and looked through a microscope at pond water when I was in elementary school, but it was actually taking
care of a patient in medical school that really helped direct me into pathology and if I can give that story. I was a third year medical student and hadn’t really decided on a specialty. And was considering a number of different specialties, including medicine and internal medicine. Pathology wasn’t so high on the list until there was an occurrence with one patient and she was on the internal medicine ward and she had rib pain. The radiologists were able to identify a lesion in the rib and the differential diagnosis that was considered clinically and the radiologist considered was quite lengthy so it really took a biopsy which then went to surgical pathology and in order to establish the diagnosis, so I went down to surgical pathology. The laboratory where the attending surgical pathologist was looking, at slides with their resident on the service and I asked if they had seen the biopsy from this particular patient and he said he had, and then he pulled out the slide and went through it and in pretty
short order said oh, 
this is metastatic cancer from 
the salivary gland, 
which was a diagnosis that was not 
really considered in this patient. 
It turns out she did have a history of 
salivary gland cancer 10 years prior 
so it occurred to me that this was 
the way to really help patients 
by helping render diagnosis. 
I find that fascinating, because certainly 
if you had a patient with rib pain, 
metastatic cancer from a salivary 
gland would not be top of the list. 
Did the pathologist know about the distant 
diagnosis of salivary gland cancer? 
I think this particular 
cancer was so distinctive that 
he was able to suspect salivary 
gland cancer right away. 
I’m not sure if he knew the history, 
but he was an excellent 
surgical pathologist and being 
an excellent surgical pathologist 
I’m sure he had asked the 
resident for the history first, 
as they examined the slide. 
Yeah, it’s just absolutely fascinating, 
but now you’ve kind of transitioned 
still looking at cancers, 
but now you’re into the world
0:03:56.178 –> 0:03:58.401 of genitourinary pathology,
0:03:58.401 –> 0:04:01.129 tell us a little bit more about how
0:04:01.129 –> 0:04:03.91 your interests transitioned to that.
0:04:06.7 –> 0:04:09.52 In residency a big
0:04:09.52 –> 0:04:11.776 part of pathology residency,
0:04:11.78 –> 0:04:13.32 which is pretty broad based,
0:04:13.32 –> 0:04:17.352 we rotate through a number of different
0:04:17.352 –> 0:04:19.626 services, subspecialty services and
0:04:19.626 –> 0:04:22.356 those services work with specific
0:04:22.36 –> 0:04:25 clinicians and it’s disease
0:04:25 –> 0:04:28.717 focused and usually organ site
0:04:28.72 –> 0:04:32.05 focused. For example,
0:04:32.05 –> 0:04:34.29 as a genitourinary pathologist,
0:04:34.29 –> 0:04:37.71 I interact very closely with the
0:04:37.71 –> 0:04:39.99 urologist and medical oncologist
0:04:40.078 –> 0:04:43.052 to treat urological cancers as well
0:04:43.052 –> 0:04:45.324 as radiologist and interventional
0:04:45.324 –> 0:04:47.342 radiologists to deal with these
0:04:47.342 –> 0:04:48.812 type of cancers and specifically
0:04:48.812 –> 0:04:50.609 for the genitourinary system,
0:04:50.61 –> 0:04:53.34 this is just an introduction.
0:04:53.34 –> 0:04:57.267 We basically address cancers that arise in
0:04:57.267 –> 0:05:01.239 the prostate and testis and bladder and
0:05:01.24 –> 0:05:06.288 kidney, so it turns out when you are
0:05:06.29 –> 0:05:07.808 in formative years,
0:05:07.808 –> 0:05:10.338 one should never underestimate
0:05:10.338 –> 0:05:13.808 how a single patient or a physician
0:05:13.808 –> 0:05:17.575 can impact the development of
0:05:17.575 –> 0:05:20.42 the individuals who are young and
0:05:20.42 –> 0:05:22.83 deciding in medical school or pathology.
0:05:24.57 –> 0:05:27.762 So I was a first year resident and
I rotated through the VA hospital which was right across from Duke University Hospital, which is where I did my residency. And there was a fascinating rotation, and another excellent surgical pathologist was the attending there, and we saw quite a lot of prostate cancer. And at the VA hospital, this was several decades ago, dating myself a number of decades ago, there was not much known about prostate cancer, and treatments were relatively limited, so it seemed to me that this was an area where there is much to be learned about diagnosis and prognosis as well as treatment of that particular cancer. So that’s really how I became interested as a first year pathology resident in genitourinary cancers, and specifically prostate cancer. Let’s dive a little bit more into prostate cancer. I think that so much of again, what we do is really dictated by the biopsies that we take. So if somebody has a mass in the prostate or an enlarged
prostate, even more globally, sometimes a biopsy will be done, and that’ll be sent to the pathologist and it’s really up to you to try to figure out is this cancer or is this something benign? And if it’s cancer, how bad of a cancer is it which really dictates is this something that we treat at all, or something that we simply watch? How do you make those decisions? How do you make that differentiation from benign to malignant and within malignant, the different grades of prostate cancer? So it’s really quite a long educational process to be able to diagnose benign versus malignant, and it turns out that what’s so fascinating is that every single biopsy is different, even if we render an umbrella diagnosis of benign tissue. For example, the lining tissue of the prostate. There could be a number of benign mimicker’s in there, meaning benign tissue looking like cancer under the microscope, but it’s not, and we have a differential diagnosis. We consider a number of different benign entities before deciding
on a malignant diagnosis, because that’s such a huge step to take for us and for the patient and the patient’s treating physician. So that’s what I particularly enjoy, that diagnostic work and it can be arduous sometimes. Sometimes it’s very straightforward that a particular biopsy is benign and sometimes straightforward that it’s malignant, but other times there are benign conditions under the microscope that look like cancer and cancer that can look benign. So we’ve been fortunate in this area to have some tools to help us and those include antibodies that can help us recognize specific cells under the microscope and in certain cases that can be relayed to us, but it still requires judgment and having formed a differential diagnosis or consideration of what’s possible before we order those tests. On that issue, so once having established a diagnosis of malignancy, then the next step is to decide and this is so important for prostate cancer, how aggressive is it? Because it turns out most men who
0:09:15.797 –> 0:09:17.83 have prostate cancer will die
0:09:17.83 –> 0:09:19.87 with it rather than of it.
0:09:19.87 –> 0:09:22.579 So there are a large number of
0:09:22.579 –> 0:09:24.517 prostate cancers that can grow
0:09:24.517 –> 0:09:26.617 very slowly and may not affect
0:09:26.617 –> 0:09:29.18 the man during his lifetime,
0:09:29.18 –> 0:09:31.23 yet it turns out that
0:09:31.23 –> 0:09:34.428 prostate cancer is the second most
0:09:34.428 –> 0:09:36.97 lethal cancer amongst American men
0:09:36.97 –> 0:09:38.311 by total numbers
0:09:38.311 –> 0:09:40.546 trailing only lung cancer.
0:09:40.55 –> 0:09:43.259 So those are the cancers we want
0:09:43.259 –> 0:09:45.225 to specifically separate out from
0:09:45.225 –> 0:09:47.065 the more slowly growing ones.
0:09:47.07 –> 0:09:49.485 And we do that under the microscope
0:09:49.485 –> 0:09:52.001 using a very powerful approach
0:09:52.001 –> 0:09:54.527 that is grade, as you suggest.
0:09:54.53 –> 0:09:56.51 So what is grade?
0:09:56.51 –> 0:09:59.144 It’s basically the way the cells
0:09:59.144 –> 0:10:01.37 grow within the prostate once
0:10:01.37 –> 0:10:04.34 we’ve identified them as cancer cells,
0:10:04.34 –> 0:10:06.279 so we can look under the microscope
0:10:06.279 –> 0:10:07.11 and in their patterns
0:10:07.11 –> 0:10:09.545 there are specific patterns that
0:10:09.545 –> 0:10:12.52 are known to correlate with the
0:10:12.52 –> 0:10:14.34 outcome for the patient,
0:10:14.34 –> 0:10:17.416 and so we have various tiers,
0:10:17.416 –> 0:10:20.246 various numbers we can apply
0:10:20.25 –> 0:10:22.294 and the most simple one that we
0:10:22.294 –> 0:10:24.458 use right now is grade group and
0:10:24.458 –> 0:10:26.288 that ranges from one to five.
One being the best outcome, and those patients are managed very differently from those who have a grade group five out of five, but there’s everything in between, so it’s really a spectrum. And therein lies again judgment as far as deciphering the detective work deciphering the patterns that can help us assign a grade that indicates aggressiveness of prostate cancer.

One of the questions that I think always comes up is that it seems to be a little bit of art and a little bit of science. Looking at these patterns and trying to decipher is this lower grade? Is this a higher grade? How much of it is art, and how much of it is science and how sure are you at any given time of your diagnosis being correct? Interpretation of slides under the microscope is most definitely both art and science, so there’s much experience that one must have in order to recognize these patterns.
The science part is that we can use antibodies to help identify specific cells. The grading part remains, though, very much art and pattern recognition going forward in the future, and this has already started. We have tools that can help us recognize patterns even better and more quantitatively, and that’s through the use of artificial intelligence and machine learning. So all of that work has just started, but already I’ve had the opportunity to work in on a couple different projects and it turns out that the computer with specific algorithms can identify, can diagnose and grade prostate cancers just as well as a number of us who specialize in sub specializing in that particular area. I can’t wait to learn more about that, but first we need to take a short break for medical minute.

Please stay tuned to learn more about prostate cancer diagnosis and prognosis with my guest doctor Peter Humphrey. Funding for Yale Cancer Answers comes from AstraZeneca, dedicated to advancing options and providing hope for people living with cancer. More information at
The American Cancer Society estimates that nearly 150,000 people in the US will be diagnosed with colorectal cancer this year alone. When detected early, colorectal cancer is easily treated and highly curable and men and women over the age of 45 should have regular colonoscopies to screen for the disease. Patients with colorectal cancer have more hope than ever before, thanks to increased access to advanced therapies and specialized care. Clinical trials are currently underway at federally designated Comprehensive Cancer Centers. Such as Yale Cancer Center and at Smilow Cancer Hospital to test innovative new treatments for colorectal cancer. Tumor gene analysis has helped improve management of colorectal cancer by identifying the patients most likely to benefit from chemotherapy and newer targeted agents, resulting in more patient specific treatment. More information is available at yalecancercenter.org. You’re listening to Connecticut Public Radio. Welcome back to Yale Cancer Answers.
This is doctor Anees Chagpar and I’m joined tonight by my guest doctor Peter Humphrey. We’re talking about prostate cancer diagnosis and prognosis, and right before the break we were talking about this magic that happens in the pathology lab. At least, it seems like magic to those of us who send them biopsies and magically get back a diagnosis that we then use to treat our patients and Doctor Humphrey was telling us that this is in part art, but it is in part science and that you’re able to use antibodies and so on to help you in making that diagnosis and right before the break you started to talk about artificial intelligence and how this might actually help us in making a diagnosis now, so that the computers might be able to make a diagnosis almost as well as an experienced pathologist. Tell us a little bit more about that. So we are in the very early pilot stage I would say as far as development of this tool, but I think it will be an important tool that can assist the pathologist and actually artificial intelligence
is being developed in many branches of medicine and radiology too, so it turns out that those parts of medicine that deal with diagnostic images like radiology and pathology are areas where there could be great benefit. From more standardization, I would say, and perhaps even quantitation, using computer assisted methods, so that’s already happening and actually happening very quickly as far as the research into this. And the use of computers and artificial intelligence. To develop algorithms, ways in which the computer can diagnose and even grade prostate cancer. So I’ve been fortunate enough to have been involved in a couple of these research studies and a number of us from around the world who are interested in prostate cancer and are genitourinary pathologists, and we’ve looked at hundreds of slides, all online, so these are all images diagnosable on our computer. And then we tested the algorithm and then the algorithm was tested against our diagnosis in grade versus collections
of pathologists who were not sub specialized in prostate cancer diagnosis and the computer was actually just as good as our diagnosis and grading. So what does this mean for the future? Well, there are actually a lot of challenges. There are several algorithms that have already been published. Methods that the computer uses, and there’s a lot of standardization and validation that needs to occur so that a computer can use images from a particular laboratory and one particular hospital as far as the scanners they use to make those images and the way the slides are prepared that all of those factors can have a huge impact on the success or failure of the algorithms. My hope is that as far as standardization, it can be used as a tool to help hospitals where there may not be ready access to a genitourinary pathologist. And also I think for those of us who have high volumes and have a special sub specialized group of Geo pathologist as we do here at Yale, I think it might actually help us screen cases. So that the computer could actually help
identify through all these slides, identify the ones that need particular attention or standardized grading. So there may be, for example, a difference of opinion about the grade of a specific cancer and the way we currently address this. And this is very important actually when there's a difficult case, we'll have a consensus conference, meaning that up to seven of us who are sub specialized in genitourinary pathology at Yale will meet around the microscope or in this area, from our computers and look at the images together to try to agree on a particular grade. In a difficult case or where it's a borderline case between grades for example. So maybe the computer could also provide help in standardizing those. Those sorts of assessments when it's a difficult or borderline case, it sounds like this is really exciting technology that might be able to provide a second opinion. But for right now, if you're a patient and you might not be at or near a large academic center, and you get a prostate biopsy, for example, how important is it for
you to get a second opinion on that biopsy from another human pathologist
if a computer isn’t readily available?
That’s a really critical question, and I think it’s important to know in discussions with your physician whether a genitourinary pathologist has reviewed the slides and it’s true that around the country there are just varying degrees of practice and varying volumes of practice, and so at a smaller hospital, maybe only a few prostate biopsies might be seen over a long period of time, and particularly in those cases where the pathologists may not feel as comfortable, or the treating physician may not feel as comfortable, it’s I think a useful step to seek a second opinion, and we see slides for second opinions all the time here from everyone. Actually from patients from treating physicians and from pathologists themselves, and this is an important quality to all these second opinions. And again we very commonly almost on a daily basis share cases here at Yale amongst our group of seven genitourinary pathologists and so are these second opinions when...
you go and you have your slides reviewed by somebody else? Or maybe the pathologists themselves sends it to another center to get reviewed if they’re not quite sure about the diagnosis, is that covered by your insurance? Usually it is. So at least the cases that we receive here for second opinions. That’s good to know. Is it ever the case where even if you go to a large academic center that it’s worthwhile getting your slides reviewed by another large academic center? I mean, how much heterogeneity is there between experienced genitourinary pathologists for example? So since diagnosis and grading are still art, there can be differences of opinion amongst even expert and experienced genitourinary pathologists and these tend to be the rarer or more borderline cases. There’s been a lot of research looking at variations or differences of opinion between pathologists and even between genitourinary pathologists, and even did a study where I looked at agreement with myself so I
diagnosed and graded some slides and then came back sometime later to see if the diagnosis and grading were the same so the agreement is pretty good amongst genitourinary pathologists, but one should not hesitate in seeking a second opinion at another center with an established group of pathologists, but as we talk about that variability, all of these pathologists are looking at the same slides and I know that in other cancers we’ve talked on this show about this concept of heterogeneity that you might have a cancer that looks kind of different in one part than another and so I wonder, when you get these biopsies, we often send a core biopsy so a sampling of this tumor, how representative is that, and is it ever the case where you look at this and you kind of say I don’t know that this is representative? We need to get more tissue or are you usually pretty happy with the sample that you get? So that’s such a key question and
really the practice of the biopsy as far as the prostate has changed so remarkably since when I was a resident.

So back in the olden days, it was usually just one needle biopsy, digitally directed towards a palpable mass in the prostate by the examining physician and one single core was taken.

So prostate cancer, heterogeneous concept of heterogeneity, and different areas of the prostate being actually of different grades and different aggressiveness is actually characteristic of prostate cancer and prostate cancer also tends to have multiple nodules within the same gland, so what’s been a real advantage is medical advances in radiology, and there are expert radiologists here who have actually helped develop this technique, and that’s a special type of MRI. Magnetic resonance imaging that’s used with ultrasound to guide the needle placement within the prostate, So now rather than one needle core, we often receive anywhere from 20 to even 30 individual needle cores per patient. And the reason is that the radiologist now can identify areas where they’re suspicious of cancer and can specifically...
say based on their grading scheme, whether they think it’s a lower risk or a higher risk case so I do feel good about the representation for most patients and when the patients have undergone this type of imaging by the radiologists. Even though multiple needle cores are placed in a single nodule, it’s still possible that maybe a smaller high grade area was missed. Warning signs would be, what if the patient has a really high serum PSA prostate specific antigen level? Or what if this is radiologically a very aggressive looking lesion, but we don’t see that under the microscope? Then I would worry about the needle maybe not sampling the worst of the cancer. Yeah, it goes back to that concept of being a bit of a detective that we talked about before the break and the fact that the pathologist is really a key part of this multidisciplinary team that you need to get information from. From the radiologist, from the surgeon, from the other physicians. who are involved
in the case to kind of put all of the pieces together to make sure that it all makes sense. That’s what I love about working here is working with so many bright and experienced physicians who are passionate about providing the highest level care and talking with them about what their perspective and view is on a specific patient. For example, if there is not a link made between pathology and what we see in the clinical setting that sort of correlation is vital. Going back to that patient with pain in the rib. It was absolutely essential to know that the patient had a history of cancer 10 years ago to establish firmly that cancer scene and what we would do is compare slides. That cancer in the rib biopsy was the same as the cancer in the salivary gland, so we do that commonly to look back at old slides to see if cancer has come back and we think a cancer might have come back or spread so that comparison is a really important part.
of the detective work we do. And I think the other piece that’s so important is that it’s so critical in terms of what you do, especially in prostate cancer, to really nail down how aggressive this is because it is the difference these days between having more aggressive surgery or radiation versus watchful waiting. Tell us a little bit more about how your decisions impact treatment and prognosis? After establishing a diagnosis of prostate cancer, we assign the Gleason grade or score and that is a grade number we give for every single prostate cancer needle core in every case and a great group for that particular biopsy. So if a patient had 10 positive cores with cancer in each one, we would assign an individual grade to each one, and actually I just gave a lecture this morning to the pathology residents on grading and staging. So it is one of the most critical things we do because grade is such a dominant prognostic indicator for us. For the patients physician, for everyone,
and the patient themselves. For example, a grade Group One in a patient with a lower PSA might consider along with their physician, the physician might consider active surveillance or careful monitoring of that cancer compared to a grade Group 5 where everyone would agree this patient definitely needs active therapy.

Doctor Peter Humphrey is a professor of pathology at the Yale School of Medicine. If you have questions, the address is cancer answers at yale.edu and past editions of the program are available in audio and written form at Yale Cancer Center Org. We hope you’ll join us next week to learn more about the fight against cancer here on Connecticut Public radio. Funding for Yale Cancer Answers is provided by Smilow Cancer Hospital and AstraZeneca.